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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,607	12/12/2003	Rajagopal Bakthavatchalam	60427 (72021)	1961

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,607	BAKTHAVATCHALAM ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,46,48-67,69-72 and 88-94* is/are pending in the application.

4a) Of the above claim(s) *88-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41, 46, 48-67 and 69-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/04 & 8/11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of group 4 in the reply of 1-12-06 is acknowledged. The request to reformulate group 4 taking into account of R_1 is reasonable. Therefore, group 4 is revised as below:

Group 4: Claims 41, 42, 45, 48-67 and 69-72 (part of each), drawn to compounds of the formula recited in claim 41, 54 and 65 wherein:

Z is N while W and Y are CH or CR_1;

V and X are N;

Pharmaceutical composition thereof;

classified in classes 514 and 544, various subclasses depending on substituents.

Claims 1-40, 42-45, 47, 68, 73-87 and 95-105 are cancelled.

Claims 41, 46, 48-67, 69-72 and 88-94 are pending.

Presently, claims 88-94 are held withdrawn from consideration as being drawn to the non-elected subject matter.

Therefore, only claims 41, 46, 48-67 and 69-72 are considered herein.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 41, 46, 48-67 and 69-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 recites the limitation of "*a pharmaceutically acceptable form thereof*", which has indefinite metes and bounds. Specification defines said limitation covering numerous forms such as: *salts, hydrates, solvates, crystal forms, polymorphs, chelates, non-covalent complexes, esters, clathrates and prodrugs*. Many of these forms (e.g., chelates and complexes) require a second component which is not defined or described in the specification. Other forms like *prodrugs* and *esters* constitute an indefiniteness of a situation known as "broad limitation followed by narrow limitation". Besides, many variables represent *esters* (e.g., R_1 represents "*C_1-C_4alkoxycarbonyl*"), which would be unclear if said groups could be considered as *prodrugs*.

Claims 46, 48-67 and 69-72 are rejected as being dependent on claim 41, and recite the indefinite limitation.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Written Description:** Claims 41, 46, 48-67 and 69-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 41 recites the limitation of "*a pharmaceutically acceptable form thereof*", which does not have adequate written description. The specification defines "*pharmaceutically acceptable form*" as below:

> **[0060]** "Pharmaceutically acceptable forms" of the compounds recited herein are pharmaceutically acceptable salts, hydrates, solvates, crystal forms, polymorphs, chelates, non-covalent complexes, esters, clathrates and prodrugs of such compounds. As used herein, a pharmaceutically acceptable salt is an acid or base salt that is generally considered in the art to be suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutical salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzene sulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanoic such as acetic, HOOC—$(CH_2)_n$—COOH where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein, including those listed by *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985). In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent,

> or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile, is preferred.
>
> **[0061]** A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified in vivo, following administration to a patient, to produce a compound of Formula I, II or III. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved to the parent compounds.

Note, the definition includes many forms such as: *salts, hydrates, solvates, crystal forms, polymorphs, chelates, non-covalent complexes, esters, clathrates and prodrugs*. However, the description is mostly for *salts*. There is no disclosure for the ratio of water molecule for forming *hydrates*. Likewise, there is no disclosure for solvents and their ratio for forming *solvates*. As for *crystal forms* and *polymorphs*, there is no description of the crystal structure or X-ray powder diffraction to confirm if such a crystal or any polymorph exist. Other forms like *chelates, non-covalent complexes* and *clathrates* require a second component which is not described in the specification at all. Although "*prodrugs*" is briefly described, the site of esters or other groups forming *prodrugs* is not clearly described. Thus, except *salt,* the limitation of "*a pharmaceutically acceptable form thereof*" lack a written description for other forms.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Scope of Enablement:** Claims 41, 46, 48, 54-64, 66, 67 and 69-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation and use of the claimed formula wherein Ar_1 or Ar_2 is *phenyl* or *pyridyl* group, does not reasonably provide enablement for the preparation and use of the claimed formula wherein Ar_1 or Ar_2 is another ring. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 41 recites a pyrido-pyrimidine formula having Ar_1 and Ar_2 as substituents. Variables Ar_1 and Ar_2 are independently selected from *6- to 10-membered aryl groups and 5- to 10-membered heterocycles*. As defined in the specification, aryl groups and heterocycles cover an extensive number of rings, see the following excerpt:

> **[0077]** A "carbocycle" or "carbocyclic group" comprises at least one ring formed entirely by carbon-carbon bonds (referred to herein as a carbocyclic ring), and does not contain a heterocyclic ring. Unless otherwise specified, each carbocyclic ring within a carbocycle may be saturated, partially saturated or aromatic. A carbocycle generally has from 1 to 3 fused, pendant or spiro rings; carbocycles within certain embodiments have one ring or two fused rings. Typically, each ring contains from 3 to 8 ring members (i.e., C_3-C_8); C_5-C_7 rings are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain representative carbocycles are cycloalkyl (i.e., groups that comprise saturated and/or partially saturated rings, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of any of the foregoing, such as cyclohexenyl). Other carbocycles are aryl (i.e., contain at least one aromatic carbocyclic ring). Such

carbocycles include, for example, phenyl, naphthyl, fluorenyl, indanyl and 1,2,3,4-tetrahydro-naphthyl.

[0078] Certain carbocycles recited herein are C_6-C_{10}arylC_0-C_8alkyl groups (i.e., groups in which a carbocyclic group comprising at least one aromatic ring is linked via a direct bond or a C_1-C_8alkyl group). Such groups include, for example, phenyl and indanyl, as well as groups in which either of the foregoing is linked via C_1-C_8alkyl, preferably via C_1-C_4alkyl. Phenyl groups linked via a direct bond or alkyl group may be designated phenylC_0-C_8alkyl (e.g., benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl). A phenylC_0-C_8alkoxy group is a phenyl ring linked via an oxygen bridge or an alkoxy group having from 1 to 8 carbon atoms (e.g., phenoxy or benzoxy).

[0079] A "heterocycle" or "heterocyclic group" has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (i.e., one or more ring atoms is a heteroatom, with the remaining ring atoms being carbon). Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 3 to 8 ring members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments) and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain heterocycles comprise a sulfur atom as a ring member; in certain embodiments, the sulfur atom is oxidized to SO or SO_2. Heterocycles may be optionally substituted with a variety of substituents, as indicated. Unless otherwise specified, a heterocycle may be a heterocycloalkyl group (i.e., each ring is saturated or partially saturated) or a heteroaryl group (i.e., at least one ring within the group is aromatic). A heterocyclic group may generally be linked via any ring or substituent atom, provided that a stable compound results. N-linked heterocyclic groups are linked via a component nitrogen atom.

> **[0080]** Heterocyclic groups include, for example, azepanyl, azocinyl, benzimidazolyl, benzimidazolinyl, benzisothiazolyl, benzisoxazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzothiazolyl, benztetrazolyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dihydrofuro[2,3-b]tetrahydrofuranyl, dihydroisoquinolinyl, dihydrotetrahydrofuranyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, dithiazinyl, furanyl, furazanyl, imidazolinyl, imidazolidinyl, imidazolyl, indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isothiazolyl, isoxazolyl, isoquinolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, oxazolidinyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, piperidinyl, piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridooxazolyl, pyridothiazolyl, pyridyl, pyrimidyl, pyrrolidinyl, pyrrolidonyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiadiazinyl, thiadiazolyl, thiazolyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thienyl, thiophenyl, thiomorpholinyl and variants thereof in which the sulfur atom is oxidized, triazinyl, and any of the foregoing that are substituted with from 1 to 4 substituents as described above.

Thus, claim 41 recites a Markush group that encompasses compounds beyond the scope of the *pyrido[2,3-d]pyrimidine* core. Thus, the scope of claim 41 is unduly broad.

Claims 46 and 48 depend on claim 41 for the scope of Ar_1 and Ar_2, and thus their scopes are also unduly broad.

Claims 54, 66 and 67 recite Ar_1 representing phenyl or pyridyl group, but they still recite Ar_2 repesenting phenyl, pyridyl or pyridazinyl group. Although scopes of claims 54, 66 and 67 are narrower than that of claim 41, they still recite compounds of *pyrido[2,3-d]pyrimidine* substituted with a *pyridazinyl* group which do not share the same biological property since

pyridazinyl ring is not art-recognized equivalent of phenyl or pyridyl ring. Thus, scope fo claims 54, 66 and 67 are not substantiated by the instant disclosure.

Claims 55-64 depend on claim 54, and thus their scopes are also unsubstantiated.

Claims 69-72 recite a pharmaceutical composition, but depend on claim 41 for the compound. Therefore, their scopes are also unduly broad.

The amount of direction or guidance presented:

Regarding the preparation of the claimed compound, the specification provides Scheme 9 which describes the process of making a compound of *pyrido-pyrimidine* in which Ar_1 is *phenyl* or *pyridyl* while Ar_2 is *phenyl*. All *pyrido[2,3-d]pyrimidine* species have Ar_1 as *phenyl* or *pyridyl*, and Ar_2 as *phenyl*. Regarding biological activity, the specification describes many bioassays, but does not disclose which compounds have been tested. Assuming all *pyrido[2,3-d]pyrimidine* species have been tested, one cannot exatrapolate the biological activity of those species to *pyrido[2,3-d]pyrimidine* compounds having Ar_1 and Ar_2 representing another ring because a ring other than phenyl or pyridyl ring could alter the configuration of the claimed compound, and thus, could change the biological activity as well. Therefore, the specification does not provide adequate enablement for the scope of the *pyrido[2,3-d]pyrimidine* formula as recited in the above claims.

The state of the prior art:

As evident by the teachings of **Meyer et. al.** (US 4,621,082) and **Bratz et. al.** (US 5,597,776), the substituents on the *pyrido[2,3-d]pyrimidine* ring can result in the activity of renal vasodilating and diuretic action, or they can result in the herbicidal activity which would be toxic

to animals and/or human. Thus, the state of the prior art does not support a large range of substituents for the same biological activity.

The relative skill of those in the art:

Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of the claimed formula. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only shows evidence that a small group of *pyrido[2,3-d]pyrimidine* compounds (substituted with a phenyl or pyridyl group) can antagonize VR1, and treat pain. However, said evidence does not adequately guide the skilled clinician to select other compounds of *pyrido[2,3-d]pyrimidine* compounds to treat pain.

Thus, with such a limited teaching, the skilled clinician would have to engage in undue experimentation to use the claimed compounds in the methods recited in the above claims.

No pending claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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2-18-06

Tamthom N. Truong
Examiner
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